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PATHOPHYSIOLOGY OF THE ALCOHOL WITHDRAWAL SYNDROME

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ABSTRACT

A characteristic withdrawal syndrome appears following the interruption of chronic heavy consumption of alcoholic beverages. The pathophysiological elaborations of the various withdrawal signs and symptoms are considered. Among the unlikely, although plausible, pathophysiologic mechanisms of the tremulousness and skeletal muscle hyperreactivity of withdrawal is the accumulation or the sustained production of one or more circulating "toxic substances." Evidence consistent with such a mechanism includes the reported alleviation by dialysis of an impending withdrawal syndrome in alcoholic patients, the appearance of reflex hyperreactivity in withdrawing animals below the level of a chronic section of the spinal cord, and the time course of the appearance and disappearance of withdrawal syndromes. The various potential pathophysiological and neurochemical manifestations of the withdrawal illness are discussed--alterations in neural inhibition, in α-aminobutyric acid, catecholamines, acetylcholine, dopamine, prostaglandin, and in peptides. Experimental tests whereby a "toxic substance hypothesis" of withdrawal can be ruled in or out are proposed.

INTRODUCTION

The signs and symptoms that appear in the period of 12-36 hours following the cessation of the chronic consumption of large amounts of alcohol were identified as constituting a withdrawal, or abstinence, syndrome in the classic report by Isbell et al. (1) of experimental studies of 10 human subjects. The findings in these volunteers directly corresponded to the clinical observations of alcoholic patients by Victor and Adams (2).

Over the past fifteen years animal experiments have been used to model the counterparts of this syndrome as one primary approach to the study of alcoholism (reviewed in 3, 4, 5, 6, 7, 8, 9, 10, 11, 12).

The withdrawal syndrome appearing after the cessation of chronic alcohol ingestion or administration consists of a complex of somatic, autonomic, affective, and sensory signs and symptoms (Table 1).

TABLE 1. Withdrawal Signs and Symptoms

Somatic:
- Tremor
- Muscle jerks
- Hyperreflexia

Autonomic:
- Blood pressure increase
- Heart rate increase
- Hyperventilation
- Anorexia
- Nausea and vomiting
- Diarrhea
- Diaphoresis-sweating
- Fever

Sleep:
- Insomnia
  - delayed onset
  - disturbed quality
- Nightmares

Seizures:
- Major
- Minor

Sensory:
- Pain
- Pruritus
- Visual disturbances
- Paresthesias

Affective:
- Anxiety
- Mania
- Depression

Sensorium and Orientation:
- Agitation
- Disorientation
- Delusions
- Hallucinations

The varieties and complexities of these withdrawal signs raise a number of questions, especially of whether or not the illness has a single, prime pathophysiological mechanism or whether it represents a complex of different disease conditions. The following hypotheses are presented with the goal that these can serve as some pragmatic guides for future research on the mechanism(s) of the withdrawal syndrome.

HYPOTHESES

Hypothesis 1: The abstinence syndrome following cessation of chronic alcohol use consists of a number of relatively separate pathophysiological sequences underlying each of the major signs and symptoms.

This hypothesis is based primarily on the recognition that the time course in man of the various signs and symptoms of withdrawal differ. These time course differences were clearly recognized by Victor and Adams' early studies (2) and they are apparent in a large number of clinical investigations. Some of the earliest signs to appear after withdrawal are the muscle tremor and shakes, in association with the subjective feelings of sickness and anxiety. Some of the later and longer-lasting signs are those associated with sleep disturbances, alterations in orientation for time and place, hallucinations and fever.

Seizures are known to occur relatively early after withdrawal or can appear some days later. However, seizures are not necessarily due to withdrawal since they can derive from a number of different origins, including brain trauma, pre-existing epilepsy, subdural hematoma, etc., as well as withdrawal.

Another fact that supports the idea of different syndromes, or at least different mechanisms of the manifestations of symptoms, is the variety of signs and symptoms observed in different patients. Some patients in withdrawal reveal marked tremor and shakes, whereas others may have a lesser degree of tremor but much more severe sweats and gastrointestinal disturbances, whereas a third may manifest classic delirium tremens with hallucinations, delirium and sustained tremulousness.

Analogous variations occur in different animal strains (e.g., 13). But animal studies have not been particularly revealing with respect to the aspect of the qualitative variations in the syndrome since the bulk of the studies have utilized only a small number of somatic, usually motor, changes as measures of the withdrawal and its intensity. A caution is also in order regarding the use of the word convulsion. The animal researcher frequently describes "convulsions" and perhaps may inadvertently imply that these are analogous with seizures in man. Actually, what is seen in animals is most often hyperreactivity to stimuli exhibited by

jumping, spasmodic muscle contractions that are not necessarily generalized clonic or tonic seizures. The convulsions seen in rodents during the alcohol withdrawal can be characterized as mild clonic muscle jerks, myoclonus or reflex hyperexcitability. This is not to say that some individual animals may not have a withdrawal syndrome that culminates in a generalized seizure, which is frequently followed by death.

Although autonomic disturbances form a major component of the syndrome in the human being, these have not been usually used in animal studies. Sleep disturbances, however, have been well characterized in man and have had fairly intensive investigation in animals (e.g., 14, 15, 16).

A corrolary of this hypothesis is that experimental approaches to the mechanisms of withdrawal may be more productive if they focus on one or another of these various symptoms or signs rather than considering all of them or all of the findings in man as a single entity. Thus, the research proposal presented at the end of this article centers on the tremors, the muscle jerks, and the skeletal muscle hyperreflexia as convenient signs to investigate and as signs which comprise one of the central cluster of signs of the abstinence syndrome. These also have the distinct advantage of their ready quantitation in humans and in animals, and in the large body of knowledge about physiology and biochemistry of motor systems.

Hypothesis 2: The withdrawal signs, specifically of tremor, muscle jerks and skeletal muscle hyperreflexia, are the consequence of the appearance of a toxic substance or substances consequent to the chronic ingestion of alcohol.

There are two extensions of this hypothesis:

(a) that the withdrawal syndrome is due to the specific presence of the substance whose action becomes apparent only upon the removal of alcohol, and

(b) that this hypothesis of a toxic substance also includes the possibility that the toxicity is due not to the appearance of a new toxic agent(s), but by the disappearance of substances essential for normal functioning, i.e., of deficiency states.

It is recognized that these hypotheses are unlikely to be proven correct. They are presented because they are possible, and it is important to rule them out as major or contributory processes.

The second hypothesis is based on the fact that animals with a spinal cord section exhibit, upon the cessation of chronic alcohol administration, withdrawal syndromes in both the posterior and anterior parts of the body. This was initially demonstrated by Nosaki and Okamoto (17) and reported at the 1978 meeting of the Society for Neuroscience. (The definitive article is currently in preparation.) Recently, I undertook to reproduce the experimental findings of Nosaki and Okamoto and our pilot experiments have confirmed their observations. Specifically, there is spontaneous coordinated reflex activity in the hind quarters of rats that have had their spinal cords removed in the thoracic region (T5-T6), allowed to recover and then subjected to a week or more of administration of alcohol three or four times a day. Preliminary evidence for "withdrawal convulsion factor(s)" has been reported in mice (18).

Nosaki and Okamoto (17) reported a marked withdrawal syndrome in both the chronic spinal animals as well as in the control unsectioned animals followed in parallel. The spinal animals manifested hind limb stepping movements that began three or four hours after the alcohol was removed, became maximal at 12-16 hours after withdrawal, and gradually diminished over a number of days. This time course is exactly the same as we have obtained in our confirming studies.

As is found consistently in man and animals, the peak intensity of the withdrawal appeared 8-12 hours or more after the alcohol level in the blood had dropped to undetectable levels. The reflex hyperexcitability and spontaneous movements of withdrawal origin can be readily "treated" by further administration of alcohol, pentobarbital or chlordiazepoxide (17).

The usual explanation for the appearance of the nervous system hyperexcitability in withdrawing animals is the over-compensation of neural systems to the sustained presence of alcohol. Consequently, most of the investigations have focused on changes occurring within the nervous system itself under the assumption that the tolerance that develops with chronic use is the initial step in the sequence that gives rise to the withdrawal signs. The withdrawal syndrome, then, is viewed as the overshoot of the compensatory response of tolerance. When the alcohol is removed, these compensatory processes become unopposed and are manifested as nervous system hyperexcitability (19).

These ideas are attractive and have been derived, in large part, in analogy with the withdrawal syndrome to narcotics in which the tolerance and the abstinence syndrome are closely linked. Although there is increasing evidence of close linkage between tolerance and physical dependence on narcotics, there is little experimental evidence to support an analogous approach to physical dependence on alcohol or other sedative/hypnotics. Furthermore, the possible sites of tolerance or dependence for alcohol have not been differentiated, for example, intrinsic neural mechanisms localized at the membrane, actions at the mitochondria or other intracellular sites, integration among small networks of neurons, or as coordinated neural activity involving cortical and subcortical nuclei.

At the very least, these observations of a withdrawal syndrome at the spinal level can be taken to prove that either the withdrawal mechanisms are intrinsic rather generally to the neural system, including neurons and nerve networks in the spinal cord, or they are the consequence of systemic factors, such as a hypothetical circulating factor that impacts on the nervous system above as well as below the level of the spinal cord disruption.

DISCUSSION

Speculation on where to look for possible factors: Circulating elements

What substances or kinds of substances might be involved as a postulated circulating toxin or deficient endogenous factor? The group of agents that have had the most inquiry and remain potential candidates are the ionic shifts of calcium and magnesium. Wolfe et al. (20) and Wolfe and Victor (21) have demonstrated that during the withdrawal period there is hyperventilation, with the end result that there is a decrease in ionized calcium in blood and eventually a decrease in magnesium. These shifts of ions are accompanied by the anticipated parallel changes in their urinary excretion. During acute intoxication there is, in fact, a loss of calcium, and during recovery there is some hypocalcemia and hypomagnesemia (see also 22, 23).

The critically important information regarding these two ions, both of which are involved in regulation of neuronal excitability, has really not been obtained. What is needed is information on their intracellular and immediate extracellular concentrations over time as

intoxication takes place and then as the withdrawal syndrome unfolds. In addition, it is highly desirable to obtain information on the fluxes of these ions, that is, their movements into and out of cells, since it is well known from the studies on skeletal muscle that even in the presence of huge changes in flux the actual concentrations may not shift markedly.

This ionic hypothesis for the withdrawal syndrome is attractive and there are clinical observations with which it is consonant. Nevertheless, the clinical findings are less than precisely correlated with the electrolyte levels and they are confounded by a number of other variables. Nevertheless, this is only a partial explanation, at best, since an essential element is the stimulus that initially gives rise to the shifts. This "ionic" hypothesis is initiated by hyperventilation. Thus, the question becomes what causes the hyperventilation? Is such due to an increase in the sensitivity of the chemoreceptors of the carotid body, for example, or is it the consequence of an increase in reactivity of the respiratory center?

Moreover, if these ionic shifts are considered a likely cause, it would seem to apply with greater impact in the case of opiates since they have a much more profound depressing effect on the respiratory center and hyperventilation does occur during narcotic withdrawal. However, narcotic withdrawal is not characterized by the kinds of tremor, muscle hyperactivity and seizures that mark the alcohol withdrawal.

The postulated toxic materials might deserve names such as the "withdrawal factors or substance(s)" or the "endogenous protective factors."

Synaptic, neurohumoral systems

Although ethanol effects on various neurohumoral systems (catecholamine, acetylcholine, serotonin, dopamine, GABA) have received extensive attention, most research has been limited to either its acute action or the development of tolerance (reviewed by 6, 12, 24, and in various articles in 25). Without question, almost all of the neurohumoral systems of brain will be involved in the behavioral manifestations of withdrawal, even if there are no other more direct involvements.

The profound changes in neural activity that obviously must accompany the withdrawal syndrome have only recently been examined (reviewed in 26). Chu et al. (27) have analyzed the evoked potentials, especially auditory potentials, finding a decreased latency and facilitation of central conduction during withdrawal. Interestingly, they, like Begleiter and Projesz (28, 29), find that recovery of the neural synaptic changes may be prolonged for 3-4 weeks or longer after withdrawal from chronic alcohol.

As withdrawal developed epileptiform activity could be detected from a number of extrapyramidal sites in rats and from a wide variety of cortical and subcortical sites (30, 31). After these extensive investigations these workers concluded that although widespread, the neuroelectric activity of withdrawal was not nonspecific and suggested "the need for an additional modulatory factor to account for its generation."

Among the central nervous system mechanisms that appear to characterize the withdrawal syndrome to alcohol is the depression of inhibition, both presynaptic and postsynaptic, that has been described by Okamoto and her colleagues (32), and more selectively with barbiturates (32, 33). These experiments were carried out in cats which had previously had alcohol and then were subjected to an acute spinal cord section as surgical preparation on the day of the spinal cord studies. Nevertheless, the observation of decreased inhibition is consonant with the motor behavior observed in withdrawal, and prompts the further consideration of an interaction with alcohol with GABA mediated systems. One such system is the presynaptic inhibition which is well known to be augmented by acute alcohol administration (34-41, reviewed in 12).

Although many of the neurohumoral systems are altered by ethanol, those mediated by GABA do seem to be central, and perhaps, critically involved. Evidence for a role of GABA systems in withdrawal includes a decrease in density of low-affinity GABA receptor binding sites with chronic ethanol administration (37)--exactly the opposite of its acute actions. Volicer and Biagioni (38) and Volicer (39) have recently examined this interaction closely. In withdrawal, there is a decreased GABA binding with a decrease in affinity of the high affinity GABA receptor binding sites, suggesting increased

amount/binding of "an endogenous inhibitor of GABA binding." This last suggestion is certainly consonant with the hypothesis being presented. Recent evidence of the potentiation of GABA mediated inhibition at hippocampal and other central nervous system sites further strengthens the view of a central role of GABA in the elaboration of ethanol's actions (40, 41).

Nosaki and Okamoto (32) conclude that in addition to depression of presynaptic inhibition there is also a decrease in postsynaptic inhibition during withdrawal; but their experiments do not permit any extrapolation as to what neural transmitter systems might be involved. Such postsynaptic inhibitory systems could involve cholinergic, glycinergic, as well as GABA systems.

In addition, ethanol administered acutely or chronically has been long known to alter catecholamine release and turnover. These changes include increased turnover in withdrawal (42, 43) and possibly either decreased norepinephrine synthesis (44), increased utilization (45), or altered receptor sensitivity (cf. 46).

Withdrawal signs may actually be mediated via adrenal catecholamine function since the innervation of adrenals appears necessary for their appearance (47). The rats with denervated adrenals consumed as much ethanolic liquid diet as intact animals, yet those with adrenal denervation failed to demonstrate the characteristic convulsions, hyperexcitability, or rigid body postures after withdrawal. How such a peripheral alteration as the adrenal denervation eventually modifies the withdrawal signs remains to be defined or discovered. In Cohen et al.'s recent report (47) withdrawal is envisioned as resulting in a preganglionic sympathetic bombardment and that catecholamine biosynthesis is altered in withdrawal primarily via a trans-synaptic process. If this be the case, acute adrenal denervation should also be effective in preventing the appearance of a withdrawal syndrome. It also defines the withdrawal as originating in the central nervous system with hyperactive sympathetic outflows. In any event, these recent findings are consistent with the present hypotheses that postulate intermediary substances in the origin of the withdrawal syndrome.

adrenal glands ↑ during withdrawal

Prostaglandins

Attractive candidates for involvement in withdrawal have been identified in the areas of the fatty acids and prostaglandins. There have been reports that linoleic acid given prior to an alcohol bout will reduce hangover and perhaps withdrawal (48,49).

Related to this is the recent study showing that prostaglandin E_1 is effective in antagonizing the withdrawal in rats (50). Prostaglandin E_1 has a modest amount of central nervous system depressant effects (51), and it is conceivable that it is either a rather specific substance that may be involved in the natural withdrawal, or that it is effective primarily because of its sedative property. Thus, it might not have any specific relationship to the pathogenesis of the alcohol withdrawal syndrome.

It is of interest, nevertheless, to note that alcohol administration may be associated with an increase in prostaglandin E_1 production as this is measured in peripheral tissues. This leads to the idea that maybe there is an increase in prostaglandin production during the drinking period and a deficiency that appears during withdrawal (50). One can only speculate regarding the site and mechanism of action of a prostaglandin in view of complexities of prostaglandin biochemistries and near absence of any further information on withdrawal. The measurement of prostaglandins in the central nervous system would perhaps be of useful approach. Certainly, the charting of the responsiveness to specific neuronal elements to challenges of prostaglandins, as well as their precursors (49, 52), would be germane.

There is the possibility of involvement of other ions than calcium and magnesium, more specifically, zinc. Zinc deficiencies have some similarities to alcohol-related effects, and zinc is also an element integrally involved in fatty acid and prostaglandin synthesis and action (49).

Withdrawal secondary to cerebral blood flow changes or vice-versa?

Among the many withdrawal changes are an increase in cerebral blood flow and cerebral oxygen utilization (53). These changes in blood flow and oxygen utilization are frequently interpreted as secondary to the changes in neural activity, yet they could also be a cause of at least some of the neural hyperactivity.

Peptides

Among the vast number of possible peptides that might be considered as candidates or be involved in withdrawal vasopressin has received some attention. Crabbe and Rigter (54) examined the exaggeration of tolerance and withdrawal in animals receiving the desglycinamide fragment of lysine vasopressin.

Evidence from dialysis

A last aspect to be considered is the possibility that none of these postulated substances are the sought-after toxic substance. Just as it is known that the hangover syndrome is, in some sense, a withdrawal, it is in large part related to other materials present in the beverages, the alcohol congeners (55, 56) and perhaps sulfur-containing compounds (57). Also, the fact that individuals may manifest rather striking differences in types and amounts of fatty acids and ketones they produce after alcohol leads me to suggest that other substances, even small molecules, deserve further investigation.

Is it also possible that, like hangovers, withdrawal will be more marked with beverages that are higher in congener content or give rise to higher levels of formaldehyde/formate (58)? Withdrawal syndromes can certainly be produced by alcohol alone, but this is not to say that more profound withdrawal sickness might be associated with alcoholic beverages with higher concentrations of congeners, formaldehyde, or other substances. To date, it would appear that the variability in the clinical syndromes and perhaps the individual variability in addition are such to preclude establishing this association on the basis of retrospective clinical reports. But the possibility is certainly intriguing and worthy of further attention.

The most cogent support of the general hypothesis set forth here are the observations of Walder et al. (59) that chronic alcoholics who underwent dialysis as a treatment of their acute intoxication were not found to have the withdrawal syndromes that attending physicians had anticipated. In fact, if the alcohol withdrawal is due to the sudden removal of alcohol, one would have anticipated a rapid onset of the alcohol withdrawal in drinking chronic alcoholic patients whose blood levels of alcohol were abruptly and rapidly lowered by the dialysis. (By analogy, a severe acute withdrawal is

seen in narcotic addicts upon the administration of an opiate antagonist, such as naloxone, which competes with the narcotic at its binding sites in the central nervous system.) However, instead of the abrupt appearance of a withdrawal syndrome, the reverse occurred. Chronic alcoholics who had dialysis reportedly recovered extraordinarily rapidly, became alert, cooperative, oriented, and moreover, they ate breakfast without nausea and vomiting! In contrast, some heavy drinking patients who had hallucinations initially attributable to alcohol withdrawal were not influenced by dialysis; these were ultimately shown to be schizophrenic with hallucinations and delusions that continued unabated for months.

It is of particular interest that patients who require dialysis because of chronic kidney disease are said to neither drink, nor drink to excess. Ende and Warren (60) have just made note of this in a Letter to the Editor inquiring of other clinicians' experiences. They note that of 40 patients who they now have under dialysis therapy, 7 were found to have stopped drinking after starting hemodialysis, 21 of them never drank, and the remainder had stopped drinking long before starting dialysis. They checked these reports of their patients by measuring blood alcohol levels in a series of 294 samples; only 4 of these were positive and these were only minimal levels. They also cite a literature search which uncovered only one review article that noted that no patients had been accepted into a dialysis program and then become recognizably alcoholic.

Perhaps the single most important comment in this brief letter was the fact that the dialysis patients stated that the reason they did not drink was because "it makes me sick," that is, nauseated. Is this the result of the accumulation of toxins other than alcohol alone?

In this connection, it is worth mentioning that although fish rapidly develop tolerance to alcohol, they have not been found to exhibit any overt withdrawal syndrome after long periods of exposure to alcohol (61). One can speculate that the ingredients essential for the withdrawal in mammals are removed via the gills.

Thus, these observations on dialysis and alcohol use and abuse suggest that chronic alcohol ingestion results in materials which are likely to produce symptoms beyond just alcohol itself; conceivably dialysis removes such materials, as we are here hypothesizing.

But it needs to be remembered that dialysis may not be just removing a toxic factor. It has other effects, including influenceson trace element levels (such as rubidium, bromine, copper, aluminum, tin and cadmium), adding heparin, or introducing absorbing materials in the dialysis membranes (62).

More complex mechanisms for withdrawal include the triggering by changes in potassium levels (63) that possibly may be related to the phenomenon of kindling (64,65). In addition, responses of the nervous system to exogenous materials may be facilitated by ethanol in the fashion similar to its known effects to increase blood-brain barriers to neutral amino acids (66, see also 67).

PROPOSED EXPERIMENTAL TESTS

We are initiating experiments to test some of these hypotheses, starting with the determination of the effects of exchange transfusions between normal animals and those undergoing withdrawal from alcohol. We propose to administer alcohol in optimal doses for the development of severe withdrawal for 1-2 weeks, providing food and water ad libitum. Alcohol will then be withheld and at 12-16 hours into withdrawal approximately 1/4 to 3/4 of the blood volume will be replaced with blood from nondependent animals. Conversely, the removed blood will be administered to normal animals who have served as the nondependent donors.

We anticipate, in accord with the hypotheses, that the animals receiving blood from the withdrawing subjects will exhibit at least some motor hyperactivity, and conversely, that the normal animals who are transfused will exhibit a much less severe withdrawal than the untreated withdrawing animals.

The second set of experiments will be analogous studies utilizing chronic spinal preparations, both as controls and those who have been addicted chronically to alcohol. We project that the chronic spinal animals will exhibit approximately the same results as the intact preparations, that is, withdrawal signs in both segments of body that is ameliorated by exchange transfusion.

As with all hypotheses, an experiment that can unambiguously test its validity is the most valuable. The experiments proposed here have that potential. It is also conceivable that the hypotheses will be shown

to be untenable, e.g., that exchange transfusion does not transfer or attenuate the withdrawal syndrome. Such a result suggests, but doesn't prove, that the withdrawal mechanisms are intrinsic to the nervous system--the conception that is commonly held. With either result, promising leads for future investigation encompass the determination of neural bases of the hyperreflexia of withdrawal, i.e., how the relative absence of pre- and of postsynaptic inhibitions (31) actually develops.

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